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TMEM106B: a strong FTLD disease modifier

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Genome-wide association studies (GWAS) are a very powerful approach for identifying novel loci associated with disease risk or other complex traits. In these studies millions of common single-nucleotide polymorphisms (SNPs), distributed across the whole genome, are analyzed for their association against disease status. The power of these studies is that it is not necessary to have an *a priori* hypothesis about the potential implication of any particular gene with disease status. This approach has successfully identified novel genes implicated in several neurodegenerative diseases including Alzheimer's disease [7], Parkinson's disease [8], frontotemporal dementia [13], progressive supranuclear palsy [6], and others. The importance of these studies is the identification of novel genes and pathways implicated in disease. The identification of these genes have led to a better understanding of disease pathogenesis and the potential identification of novel biomarkers and therapeutic targets.

In early 2010, a GWAS performed in 426 autopsy-confirmed frontotemporal lobar degeneration (FTLD) with TAR DNA-binding protein (TDP-43) inclusions cases, 89 granulin (GRN) mutation carriers and 2,509 population controls, identified *TMEM106B* (top SNP rs1990622, $P = 1.08 \times 10^{-11}$; odds ratio, minor allele (C) 0.61, 95% CI 0.53–0.71) as a risk factor for FTLD-TDP [13]. Several single nucleotide polymorphism (SNPs) are in linkage disequilibrium with rs1990622, including rs3173615 (minor allele G), a *TMEM106B* non-synonymous variant (p.T185S) [2,4]. Interestingly, the association of *TMEM106B* with FTLD risk was stronger in the *GRN* mutation carriers (n=89) than in the autopsy-confirmed cases (n=426). In the autopsy-confirmed cases, the *TMEM106B* locus was the strongest signal but did not reach the genome-wide significant threshold [13]. The role of *TMEM106B* in FTLD-TDP, or even the normal biological function of *TMEM106B*, was unknown at that time. But based on these findings, it was hypothesized that *TMEM106B* affects risk for FTLD-TDP by affecting *GRN* levels [2,4,13]. Subsequent studies demonstrated that the p.T185S variant presents slower protein degradation that leads to higher steady-state *TMEM106B* levels [9], the risk allele was associated with lower GRN protein levels and early age at onset in *GRN* mutation carriers [2,4], and that increased expression of TMEM106B leads to alterations in the intracellular vs. extracellular partitioning of GRN [1]. These results suggested that *TMEM106B* alters the disease risk among GRN mutation carriers by modulating GRN protein levels.

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In 2010, mutations in *GRN* were the most common known genetic cause of FTLD. However in late 2011, the *C9ORF72* expansion repeat emerged as the major cause of FTLD [3,11] (also see the Alzheimer Disease & Frontotemporal Dementia Mutation Database: http://www.molgen.ua.ac.be/ADMutations/). Since then, several research groups have been interested in determining whether the *TMEM106B* was also a risk factor or a disease modifier in *C9ORF72* expansion carriers.

In this issue of Acta Neuropathologica, two independent groups analyzed the association of *TMEM106B* variants with disease risk, age at onset, and age at death in *C9ORF72* expansion carriers [5,12]. At first, it may look like the results from these studies are contradictory. However, these studies are in fact complementary and represent an independent replication of each others findings. The reason why the results appear contradictory is because the authors focus their results on two different SNPs (rs1990622 and rs3173615) and different genetic models (additive vs recessive, or major allele as reference vs. minor allele) to perform their analyses and because one of these studies concentrated on age at onset and age at death, whereas the other focused on disease risk. In this brief commentary, we will go through the results and tables trying to harmonize the results, so it will be easier for readers to interpret both studies.

The first big difference between the Gallagher et al.,[5] and the Van Blitterswijk et al., [12] studies is that the first study focused on rs1990622 (T/C SNPs, C minor allele) while the second one focused on rs3173615 (p.T185S, C/G SNPs, G minor allele). Both SNPs are in LD (D'=1, R^2 =1), therefore the rs1990622-C allele is comparable to the rs3173615-G allele. In fact, Van Blitterswijk et al., also analyzed rs1990622 finding the same results as with rs3171615.

The second important difference is that Gallagher et al., (rs1990622, C-minor allele) calculated the Odds Ratio (OR) for disease risk for the major allele (T), whereas Van Blitterswijk et al., calculated the OR for the minor allele (G). This explains why in Gallagher et al., the OR>1 (the carriers for the major allele present higher risk) and the OR is <1 in Van Blitterswijk et al. (the minor allele is protective, which is the same as saying major allele carriers present higher risk (table 1)). A third difference is that Gallagher et al. used an allelic model to analyze the association of the *TMEM106B* SNP with disease risk, but Van Blitterswijk et al. used a recessive model respective to the minor allele (minor allele homozygous vs. heterozygous and major allele homozygous). Van Blitterswijk et al. decided to use this model because in their present and previous studies the recessive model presented the best fit [4]. Regardless of these differences, both studies found very comparable minor allele frequencies (MAF) in cases and controls, and additionally, found that *TMEM106B* SNPs are strongly associated with disease risk (table 1) (see table 2 and 3 of Van Bitterswijk et al., and Gallagher et al., respectively).

Comparison of the results for age at onset may seem confusing as well. Gallagher et al., report the results for an additive genotypic model (table 1 and 2 of Gallagher et al.), but a dominant genotypic model is used in the survival analysis and figures. The dominant model is in relation to the major allele (major allele homozygous and heterozygous vs. minor allele homozygous), which is the same comparison as a recessive model for the minor allele. In

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this case, Gallagher et al., found that the minor allele homozygotes present with a significantly lower age at onset and age at death (see results, table 1, 2 and figure 1 of Gallagher et al.). Similarly, Van Blitterswijk et al., also found that the minor allele homozygotes present with a lower age at onset, but it is important to highlight that this finding did not approach significance, and that they grouped all *C9ORF72* expansion carriers (also MND patients) for their age at onset analysis, which may account for some of the differences between the two studies. The findings related to age at onset, therefore, are not conclusive and more studies and/or meta-analyses are needed to confirm this potential association.

Based on the combined results from the papers published in this issue of Acta Neuropathologica (table 2), the effect of the *TMEM106B* SNPs in disease risk is similar in *GRN* mutation carriers (OR=0.61, [13]) and in *C9ORF72* expansion carriers (OR=0.68, table 2). As the initial study suggested that the effect of the *TMEM106B* SNPs was stronger in GRN mutation carriers, several studies were focused on analyzing the effect of TMEM106B on GRN levels [2,4] and pathways in which GRN is involved [1,10]. However it is still unknown whether TMEM106B also affects risk for disease in the *C9ORF72* expansion carriers by affecting C9ORF72 levels, any pathway in which C9ORF72 is involved, or through some unknown interaction between GRN and C9ORF72.

Another interesting finding of the Gallagher et al. study is that the minor allele, which is protective in *GRN* and *C9ORF72* expansion carriers and is also associated with later onset on *GRN* mutation carriers, may actually be associated with earlier onset and death in *C9ORF72* expansion carriers. It is known that *APOE 4* is associated with Alzheimer's disease risk and earlier onset in *APP* and *PSEN1* mutation carriers, so it is relatively common that the same genetic variant is associated with disease risk and age at onset, but it is more unusual that the same variant is associated with increased risk and later onset at the same time. The authors suggest that this may be due to a complex interplay between *TMEM106B* genotype, *C9orf72* expansion, and manifestation as ALS vs. FTD. Indeed, in a prior paper, this group has shown that *TMEM106B* genetic variants influence risk for dementia in ALS patients, without associating with ALS itself [14]. Intriguingly, the Van Blitterswijk et al. paper also sees differential association of *TMEM106B* genetic variants with *C9orf72*-associated FTD vs. ALS; specifically, in ALS patients with *C9orf72* expansions, there is no difference in *TMEM106B* genotype frequencies compared to controls. It will be necessary to perform additional genetic studies to confirm the association with age at onset and additional functional studies to determine the mechanism by which the *TMEM106B* affects risk for disease and age at onset and death in *C9ORF72* expansion carriers.

In summary, the results from Van Blitterswijk et al., and Gallagher et al., indicate that TMEM106B is a major disease modifier for frontotemporal dementia, independently of whether the disease is caused by pathogenic mutations in the *GRN* or *C9ORF72* gene.

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Table 1

Comparison of the Van Blitterswijk et al., and Gallagher et al., studies

study	SNP	minor allele	Ref. allele	model	Reported OR/Beta	OR/Beta Minor Allele
Risk for disease						
Gallagher	rs1990622	C	T	Allelic	1.56 (table 3)	0.64 (minor allele carriers>lower risk)
Van Blitterswijk	rs3173615	G	G	Recessive	0.33 (table 1)	0.33
Age at onset						
Gallagher	rs1990622	C	T	Additive	+3.47 (table 2)	−3.47 (minor allele carriers>earlier onset)
Gallagher	rs1990622	C	T	Dominant respect major allele*	–	–
Van Blitterswijk	rs3173615	G	G	Recessive respect minor allele*	−1.26 (table 3)	−1.26 (minor allele carriers>earlier onset)

Ref. Allele= reference allele.

OR= Odds ratio

* please note that a genetic dominant model (MM+Mm vs. mm) respect to the major allele is the same as a recessive model respect to the minor allele (MM+Mm vs. mm). “M” denotes major allele and “m” minor allele